NTP
National Toxicology Program

Peer Review of Draft Substance Profiles for the 12th Report on Carcinogens

Mary S. Wolfe, Ph.D.
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
Research Triangle Park, NC
June 21-22, 2010

Topics

- Report on Carcinogens (RoC)
- 12th RoC review process
- Peer review format and charge

RoC

- Provides information about potential cancer hazards in our environment
- Hazard identification document
  - Identifies agents, substances, mixtures, or exposure circumstances that may pose a carcinogenic hazard for people in the United States
  - Lists "substances" as *known* or *reasonably anticipated human carcinogens*
- Congressionally mandated biennial report
  - Secretary, Health and Human Services (HHS), has responsibility for the report
  - 1st RoC published in 1980 had 26 listings
  - Current 11th RoC has 246 listings (58 *known* and 188 *reasonably anticipated*)

Substance Profiles

Substance Profiles

Polychlorinated Biphenyls (PCBs)
CAS No. 1336-36-3

Reasonably anticipated to be a human carcinogen
First Listed in the *Second Annual Report on Carcinogens* (1981)

Carcinogenicity

Several mixtures of polychlorinated biphenyls, including Aroclor 1260 (11096-82-5), Aroclor 1254 (11097-69-1), and Kanechlor 500 (37317-41-2), are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity in experimental animals (IARC 1978, 1982, 1987, Norback and Weltman 1985). When administered in the diet, Aroclor 1260 induced liver tumors including trabecular cell carcinomas, neoplastic nodules, simple cholangiomas, and cystic cholangiomas in rats of both sexes, and hepatocellular carcinomas and liver adenocarcinomas in female rats. When rats that had undergone a partial hepatectomy were administered Aroclor 1260 in the diet, liver tumors were induced, including neoplastic nodules in both sexes and simple and cystic cholangiomas, trabecular cell carcinomas, and adenocarcinomas in females. When administered in the diet, Aroclor 1254 induced hepatomas in male mice and Kanechlor 500 induced hepatocellular carcinomas in male mice (Norback & Weltman 1985, IARC 1978).

There is inadequate evidence for the carcinogenicity of PCBs in humans (IARC 1982). A slight increase in the incidence of cancer, particularly melanoma of the skin, has been reported in a small group of men exposed occupationally to Aroclor 1254. A study of 1,310 workers with at least 6 months of exposure to polychlorinated biphenyls in a capacitor manufacturing plant showed an excess of all cancers among male workers. The excess was mainly due to cancers of the digestive system and of the lymphatic and hematopoietic tissues (IARC 1982).

Properties

Theoretically, there are 209 possible polychlorinated biphenyl isomers, although not all are found in manufactured products. Polychlorinated biphenyls vary in appearance from mobile, oily liquids to white, crystalline solids to hard, noncrystalline resins. They are thermally stable, resistant to oxidation, acids, bases, and other chemical agents, and have excellent dielectric properties. Chlorobiphenyls are colorless crystals in the pure form. Commercial products are liquids because the melting point is depressed when polychlorinated biphenyls are mixed. Polychlorinated biphenyls are practically insoluble in water and soluble in oils and organic solvents. Technical-grade polychlorinated biphenyls have varying proportions of the different chlorobenzene isomers with small amounts of polychlorinated dibenzofurans and polychlorinated naphthalenes as contaminants (IARC 1978).

Use

Since 1974, all uses of polychlorinated biphenyls in the United States have been confined to closed systems such as electrical capacitors and transformers, vacuum pumps, and gas-transmission turbines. Before 1972, polychlorinated biphenyls were used in transformer cooling liquids, heat-transfer and hydraulic fluids, vacuum pump fluids, lubricants, plasticizers, fillers in investment casting waxes, surface coatings and sealants, pesticide extenders, and carbonless copy paper (IARC 1978, Merck 1996). Currently, polychlorinated biphenyls are used by individual petitioners granted exemptions for use as a mounting medium in microscopy, as an immersion oil in low fluorescence microscopy, as an optical liquid, and for research and development (ATSDR 2000).

Production

Polychlorinated biphenyls are no longer produced in the United States, except for limited research and development applications; import and export of the compounds have not been permitted since 1979. In 1974, the Monsanto Chemical Company, which manufactured 99% of the polychlorinated biphenyls used by U.S. industry, produced an estimated 40 million lb of polychlorinated biphenyls (ATSDR 2000). Domestic production reached a peak volume of 86 million lb in 1970 and decreased to approximately 41 million lb by 1974. Polychlorinated biphenyls were first produced commercially in the United States in 1929 (IARC 1978).

Exposure

The primary routes of potential human exposure to polychlorinated biphenyls are ingestion, inhalation, and dermal contact. The release of polychlorinated biphenyls from prior industrial uses and the persistence of the compounds in the environment have resulted in widespread contamination of water and soil, with subsequent potential exposure of the general population. Polychlorinated biphenyls have been identified at 10 hazardous waste sites designated in the National Contingency Plan. EPA's Toxic Chemical Release Inventory listed 18 industrial facilities that produced, processed, or otherwise used polychlorinated biphenyls in 1999. The facilities reported releases of polychlorinated biphenyls to the land which were estimated to total 10,630,427 lb. (TRI99 2001). Polychlorinated biphenyls have been found in runoff, sediments, soil, creek water, leachate, in an underground oil-water layer, and in pond effluent. Concentrations ranged from 4 to 440,000 µg/L. The National Organics Monitoring Survey conducted from 1976 to 1977 found polychlorinated biphenyls in 6% of ground water used for drinking water at levels of 0.1 µg/L. A major source of exposure is through the diet; fish, cheese, eggs, and contaminated animal feed are the major U.S. commodities in which polychlorinated biphenyls have been found. Residues of polychlorinated biphenyls have been detected in human milk and fat samples collected from the general U.S. population (IARC 1978). In 1978, the average daily human food intake was estimated to be 0.027 µg/kg per day, but declined to <0.001 µg/kg per day in 1991 (ATSDR 2000).

Fires in and/or explosion of electrical capacitors results in contamination of nearby areas. This occurrence can result in possible human exposure through inhalation of airborne polychlorinated biphenyls or dermal contact with contaminated surfaces. Proper prevention and management of these fires can greatly reduce human exposure (EPA 1984). EPA estimated that approximately 12 million persons within 12 miles of three existing and nine projected commercial incinerators may possibly be exposed to releases of polychlorinated biphenyls in the air. In 1977, NIOSH estimated that 12,000 workers had potential occupational exposure as a result of polychlorinated biphenyls in the work environment (NIOSH 1977). Additional exposure information may be found in the ATSDR Toxicological Profile for Polychlorinated Biphenyls (ATSDR 2000).

Regulations

DOT

PCBs are considered hazardous substances and marine pollutants and special requirements have been set for marking, labeling, and transporting these materials

EPA

Clean Air Act
NESHAP: Listed as a Hazardous Air Pollutant (HAP)
Urban Air Toxics Strategy: Identified as one of 33 HAPs that present the greatest threat to public health in urban areas

Clean Water Act
Effluent Guidelines: Listed as a Toxic Pollutant
Water Quality Criteria: Based on fish/shellfish and water consumption = 0.000064 µg/L; based on fish/shellfish consumption only = 0.000064 µg/L

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable Quantity (RQ) = 1 lb

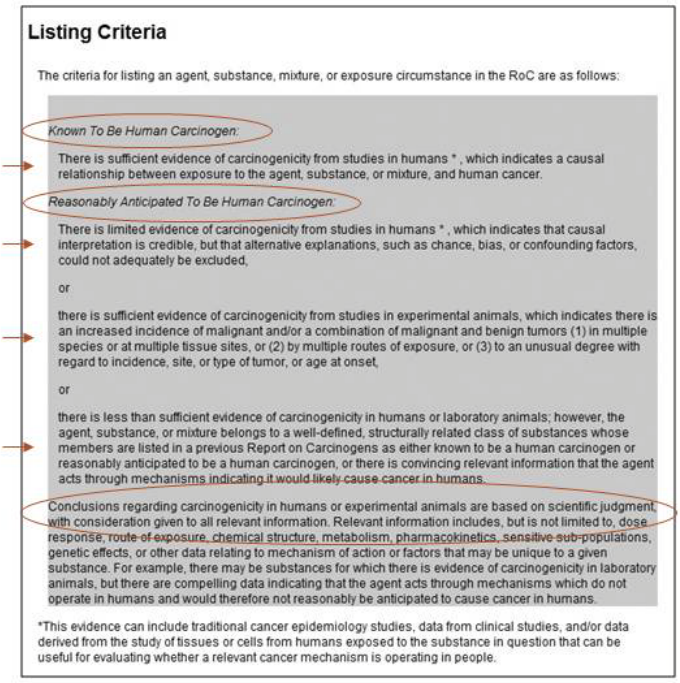
Report on Carcinogens, Eleventh Edition

- Identifies the listing
- Summarizes relevant information that supports the listing
  - Carcinogenicity, genotoxicity, and biologic mechanisms in humans and/or animals
  - Potential for human exposure
- Provides information on
  - Properties of the substance
  - Use and production
  - Current Federal regulations and guidelines to limit exposures

Preparation of the RoC

- Delegated by the Secretary, HHS, to the NTP
- NTP uses a multi-step process with multiple opportunities for public input
  - Current process released in April 2007
    - Addressed
      - Public input on process: public meeting January 2004
      - OMB Final Information Quality Guidelines for Peer Review
    - Added peer review of draft NTP documents used in the review and additional opportunities for public input
- Specific RoC listing criteria used to evaluate the scientific evidence on a substance to determine whether or not to list
  - Current criteria approved by the Secretary in 1996

RoC Listing Criteria



Listing Criteria

The criteria for listing an agent, substance, mixture, or exposure circumstance in the RoC are as follows:

Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans * , which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated To Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans * , which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,

or

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,

or

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

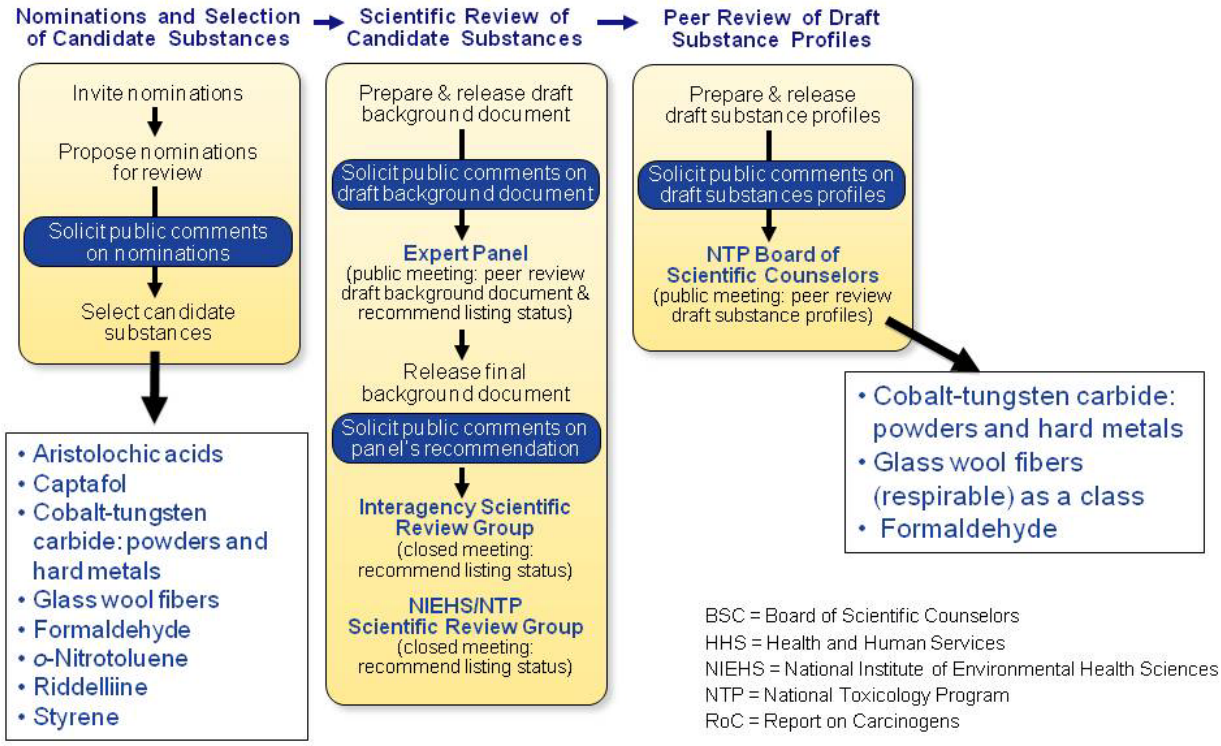
Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

- Used to evaluate the scientific evidence on a candidate substance for a listing determination
- Categories
  - List as
    - "Known"
    - "Reasonably anticipated"
  - Do not list
- Listing determination is based on the strength of the evidence
  - Specific standards that the body of scientific evidence must meet to reach a listing determination
  - Conclusion based on scientific judgment with consideration of all relevant information

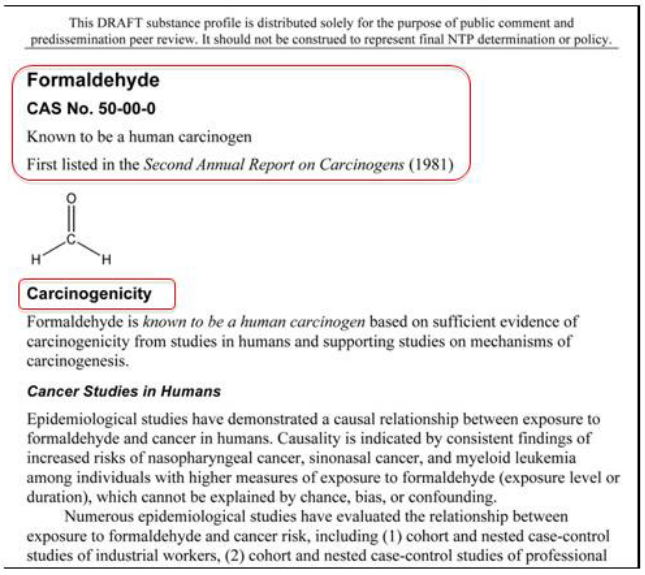
NTP
National Toxicology Program

NTP Report on Carcinogens Review Process



BSC = Board of Scientific Counselors
HHS = Health and Human Services
NIEHS = National Institute of Environmental Health Sciences
NTP = National Toxicology Program
RoC = Report on Carcinogens

Draft Substance Profile



This DRAFT substance profile is distributed solely for the purpose of public comment and predissemination peer review. It should not be construed to represent final NTP determination or policy.

Formaldehyde

CAS No. 50-00-0

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Carcinogenicity

Formaldehyde is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans and supporting studies on mechanisms of carcinogenesis.

Cancer Studies in Humans

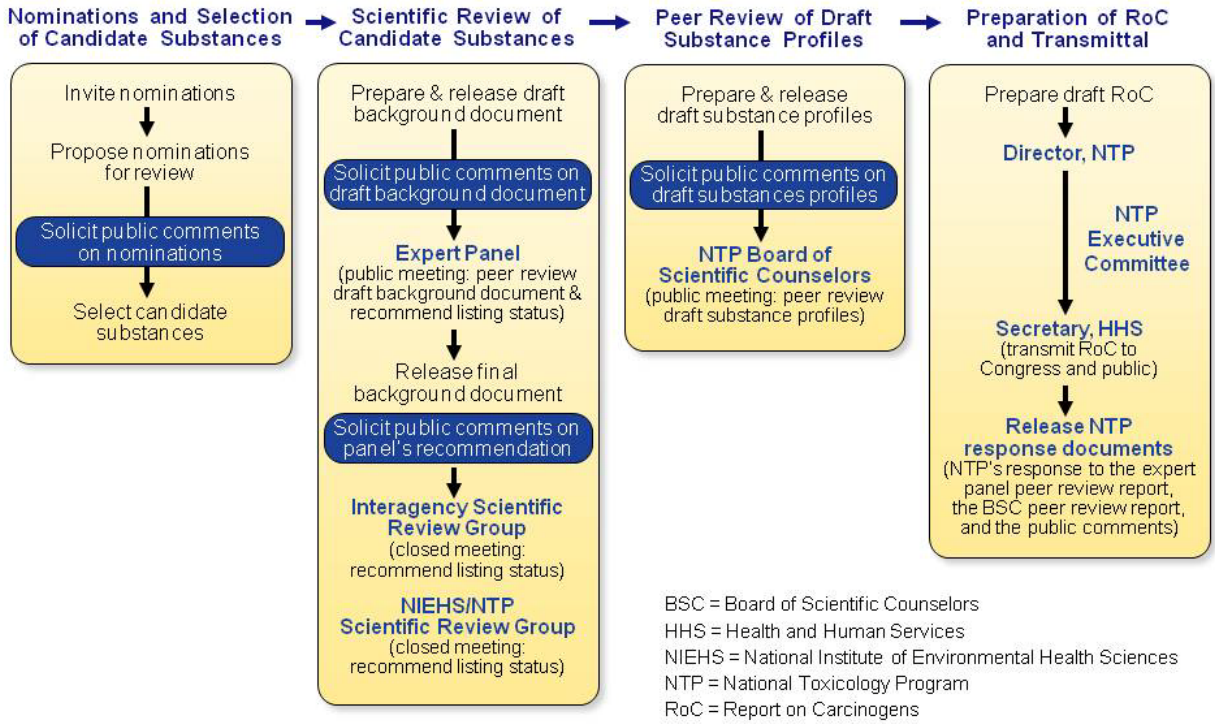
Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans. Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding.

Numerous epidemiological studies have evaluated the relationship between exposure to formaldehyde and cancer risk, including (1) cohort and nested case-control studies of industrial workers, (2) cohort and nested case-control studies of professional

- Same format as RoC substance profile
- Provides NTP's preliminary policy decision on listing status in RoC
- Summarizes scientific information supporting the listing recommendation
- Provides information on
  - Potential for exposure
  - Properties of substance, use, and production
  - Current Federal regulations

NTP
National Toxicology Program

NTP Report on Carcinogens Review Process



BSC = Board of Scientific Counselors
HHS = Health and Human Services
NIEHS = National Institute of Environmental Health Sciences
NTP = National Toxicology Program
RoC = Report on Carcinogens

Peer Review Format

- RoC staff present NTP's preliminary listing recommendation and supporting scientific information
- Public comments
- Peer review comments by reviewers – BSC and *ad hoc* reviewers
- Additional BSC comments
- BSC discussion

Charge

Determine whether the scientific information cited in the draft substance profile for a candidate substance is technically correct, clearly stated, and supports the NTP's preliminary policy decision regarding its listing in the RoC (i.e., *known to be human carcinogen* or *reasonably anticipated to be human carcinogen*, or *not to list*).